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Y.B. RADZISHEVSKA [1,2], L.Y. VASIL'EV [1],
V.G. KNIGAVKO [2], N.I. LYKHOVITSKAYA [1]

RELATIONSHIPS OF NOSOLOGICAL FORM OF THE PRIMARY AND SECOND NEOPLASMS IN ONCOLOGICAL PATIENTS

SE "Institute of Medical Radiology named after S.P. Grigoriev"
of the National Academy of Medical Sciences of Ukraine [1],
Kharkov National Medical University [2], Kharkov,
Ukraine

Цель. Исследование зависимости между нозологическими формами первых и вторых раков у пациентов, которые проходили специальное лечение по поводу онкологического заболевания и у которых возникли вторые раки через 3 года и более после окончания лечения.

Материал и методы. В исследовании проводилось сравнение между нозологической структурой вторых раков, которые возникли у 203 пациентов, проходивших лечение по поводу онкологической патологии, и официальными данными об удельном весе 10 основных нозологических форм злокачественных новообразований населения Украины. Статистическая значимость полученных результатов оценивалась с помощью доверительных интервалов, нормированных с учетом специфики контингента пациентов клиники, где проводилось исследование.

Результаты. В соответствии с удельным весом нозологических форм первых раков, обусловленных, в первую очередь, специализацией клиники, обследуемые группы пациентов были разделены на 5 нозологических подгрупп: пациенты с раком молочной железы, щитовидной железы, тела матки, шейки матки, рак яичников и с иными формами рака. Для каждой из подгрупп была исследована нозологическая структура вторых раков и сопоставлена с общей структурой злокачественных новообразований по данным официальной статистики. Показано, что частота пяти выделенных нозологических форм, рассчитанных для клиники, достаточно хорошо соответствует популяционному среднему, при этом для двух наиболее представительных нозологических форм соответствие находится в пределах ожидаемой стохастической изменчивости. Таким образом, показано, что не существует статистически значимых различий между процентным составом 10 основных нозологических форм рака населения Украины и структурой нозологических форм вторых раков у исследуемой группы пациентов.

Заключение. Нозологическая форма вторых раков не является следствием первого рака, а воспроизводит общую нозологическую структуру заболеваемости злокачественными новообразованиями.

Ключевые слова: первые раки, вторые раки, структура заболеваемости злокачественными новообразованиями, этиология вторых раков

Objective. To investigate the relationship between nosological forms of the primary and second neoplasms in patients who have undergone special treatment for cancer, and who have developed second neoplasms three and more years after the end of treatment.

Methods. The study has compared the nosological structure of second neoplasms that developed in 203 patients undergoing treatment for oncological pathology with the official data on the specific weight of 10 major nosological forms of malignant neoplasms in Ukraine. The statistical significance of the obtained results has been estimated using confidence intervals normalized taking into account the specificity of the patients of the clinic where the study was conducted.

Results. In accordance with the specific weight of the nosological forms of the primary neoplasms, conditioned first by the specialization of the clinic, the study groups were divided into 5 nosological subgroups: patients with breast, thyroid, uterine, cervical, ovarian, and subgroup with other forms of cancer. For each of the subgroups, the nosological structure of the second neoplasms was investigated and compared with the overall structure of malignant neoplasms according to the official statistics. It is shown that the frequencies of five allocated nosological forms calculated for the clinic correspond fairly well to the population mean, while for two most representative nosological forms the correspondence is within the expected stochastic variability. Thus, it has been demonstrated that there are no statistically significant differences between the percentage composition of 10 major nosological forms of cancer in Ukraine and the structure of nosological forms of second neoplasms in the study group of patients.

Conclusions. The nosological form of second neoplasms is not a consequence of the primary cancer, but reproduces the overall nosological structure of the incidence of malignant neoplasms.

Keywords: primary neoplasms, second neoplasms, incidence structure of malignant neoplasms, etiology of second cancers

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Relationships of Nosological form of the Primary and Second Neoplasms in Oncological Patients
Y.B. Radzishevska, L.Y. Vasil'ev, V.G. Knigavko, N.I. Lykhovitskaya

Introduction

Effective methods of treatment and early diagnosis have resulted in a significant increase in the survival of cancer patients. For example, in the USA, the number of patients who have survived after the primary cancer is 3.5% and increases annually by almost 1,000,000 [1]. However, against the background of a general increase in life expectancy, another problem arises sharply: the problem of the secondary cancer [2]. According to statistical data, the incidence of recurrent neoplasms in surviving patients is 16% [3, 4].

Multiple primary malignant neoplasms or polyneoplasia are simultaneous or sequential formation of malignant tumors. They develop on their own and independently of each other within one or more organs of the human body. According to S.Ya. Maximov, 75% of polyneoplasias are hormone-dependent [5].

Multiple primary malignant tumors in accordance with the terms of their detection are usually divided into synchronous and metachronous or second cancers. The fact of prevalence of metachronous tumors of all localizations over synchronous is considered to be established.

Several hypotheses have been proposed to explain the fact of multiple lesions. Thus, for example, such therapeutic effects on the primary tumor as radiation therapy, polychemotherapy and immunosuppression are viewed as risk factors for second tumors development [6]. Another theory suggests that different cancers may have the same etiological factors, while the time of the agent's action plays a decisive role in the emergence of several malignant tumors [7]. Immunodeficiency, heredity can also contribute to the development of recurrent cases of cancer in the same patient [8]. In addition, it is demonstrated that in the emergence of second neoplasms, age and sex matter [7, 8]. In particular, according to the literature data, women aged 41-60 years have a combination of hormone-dependent carcinomas [9]. It is believed that the prevalence of metachronous cancers in women compared with men is associated with a high frequency of polyneoplasia in the organs of reproductive system [8, 9].

The tendency of the body to form tumors, cancrophilia, is of great importance in the development of polyneoplasia [10, 11]. According to some reports, in 5-10% of patients who have survived the treatment of the primary cancer, the malignant process develops in another organ or tissue [11]. The Cancrophilia Syndrome includes hormonal metabolic shifts and disorders in the immune system that increase the probability of malignant transformation of cells under the influence of exogenous factors that create favorable conditions for the survival and progression of tumor clones [12, 13]. It is shown that in persons cured of malignant tumors in childhood, the risk of developing the second tumor is 10 times higher than in patients whose tumors appeared in adulthood [12].

The probability of the appearance of second tumors increases in the presence of systemic disorders and with a decrease in the body's defenses, as well as with the pronounced disturbance of homeostasis, in particular, when pro and antioxidant mechanisms are shifted toward oxidation [9, 14,]. Surgical treatment and chemoradiotherapy lead to further intensification of lipid peroxidation and to a decrease in the level of endogenous antioxidants. Thus, it becomes possible to induce the transition of the initiated cell into a transformed state, to accelerate the growth and metastasis of the primary tumor, which is explained by the significant biological and hormonal rearrangement of the body.

Ambiguous in its solution is the relationship between the nosological forms of the primary and second neoplasms. The overwhelming number of numerous foreign studies aimed at studying the problems of second neoplasms, are carried out within the framework of one primary oncological pathology and investigate the connections between the primary and second cancers, taking for the dogma the dependence of the second-cancer nosologies on the nosological form of the primary tumor [3, 16, 17].

Objective. To investigate the relationship between nosological forms of the primary and second neoplasms in patients who have undergone special treatment for cancer, and who have developed second neoplasms three and more years after the end of treatment

Methods

The study has been conducted on a multinasological block of follow-up data of 203 cancer patients undergoing treatment at the clinic of SE "Institute of Medical Radiology named after S.P. Grigoriev" of the National Academy of Medical Sciences of Ukraine (the Institute) since 1993 and who have developed second tumors three and more years after the treatment. Patients were treated according to the standard schemes that were used in accordance with the specific nosological form of the neoplasm. The schemes either included or not included surgical treatment, adjuvant and neoadjuvant radiation or chemotherapy in various combinations. When second malignant tumors developed, they were treated as primary ones. In some patients, the primary tumor was diagnosed in childhood, and at the Institute they were treated

for a second tumor and information about these patients was also taken into consideration.

The fact of the second tumors development and their nosological forms were recorded in the electronic database used in the study only if there was an appropriate record in the patient's medical history, that is, if the patient addressed for help at the Institute's clinic and was there to treat the second tumor. Since the treatment of non-melanoma skin diseases and malignant neoplasms of various parts of the intestine is not included in the list of the main areas of competence of the Institute, the history of patients with these forms of second cancer in the database has not been included or analyzed in most cases.

The median age of the patients at the onset time of the second malignant tumors was 50 years with a fluctuation from 4 years (patients with childhood cancers) to 81 years. The interquartile range of the sample was 42÷59 years. In the group there were 190 women (93.6%) and 13 (6.4%) men. The percentage composition of nosology of the primary cancers in patients with second tumors (group ST) reproduced the nosological orientation of the Institute's clinic: in 58% of patients (118) breast cancer was the primary, in 8% (17 people) – thyroid cancer, in 6% (13 people) – cancer of the uterus body, in 5% (10 people) – cervical cancer, in 4% (8 people) – ovarian cancer, in 19% (37 people) other nosological forms. The median age of appearance of other cancers in the ST group was 59 years with a fluctuation from 30 to 83 years and an interquartile range of 52÷67 years. The time interval between tumors ranged from 3 to 40 years (the lower limit in patients with childhood cancers) with a median of 7 years and an interquartile range of 4÷12 years.

The median timing of breast cancer after the treatment of the primary tumors was 7.2 years, uterine cancer – 7 years, cervical cancer – 6.7 years, ovarian cancer – 5.6 years, thyroid cancer – 10.8 years.

The nosological structure of the second tumors was compared with the official data on the specific weight of the major nosological forms of malignant neoplasms of the Ukrainian population according to the bulletin of the Ukrainian National Cancer Registry No. 16 – "Cancer in Ukraine 2013-2014". For quantitative comparison, the following simple procedure was used. A certain set of common nosological forms of malignant neoplasms was considered. Based on the total number of cases from this set, the expected number of cases was calculated on the assumption that the probability of each of the considered nosological forms is proportional to the specific weight of this form according to the data of the cancer registry. Then, based on the total and expected number of cases, the prediction intervals (95%) of the stochastic spread was calculated using the binomial distribution: the lower bound of the interval was defined as the largest number of cases for which the cumulative binomial distribution is not greater than 0.025, and the upper limit is the smallest number, for which the cumulative binomial distribution is not less than 0.975. If the actual number of cases of this nosological form exceeds the calculated interval, this indicates that the frequency of this form in the studied sample is significantly different from the expected in accordance with its specific weight in Ukraine.

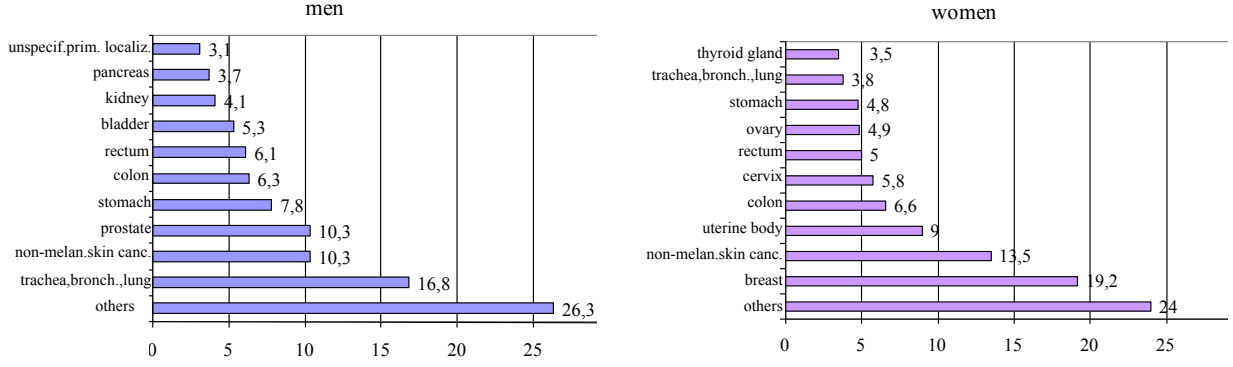
Conclusions

Based on official statistics, the most common nosological forms of cancer in Ukraine (Figure 1) were: breast (19.2%), non-melanoma malignant neoplasms (MN) of the skin (13.5%), uterine (9.0%), colon (6.6%), cervix (5.8%), rectum (5.0%), ovary (4.9%), stomach (4.8%), trachea, bronchi, lungs (3.8%), thyroid gland (3.5%), others (24.0%).

As part of the conducted study, a hypothesis has been put forward that the nosological form of second cancers is not a consequence of the primary cancer, but reproduces the overall nosological structure of the incidence of malignant neoplasms. The study of this issue consisted in comparing the structure of second cancers for each of the above nosological forms with the data of the national Cancer Registry.

Since the patients of the Institute's clinic

Fig. 1. Data of the bulletin of the Ukrainian National Cancer Registry No. 16 – «Cancer in Ukraine 2013-2014».



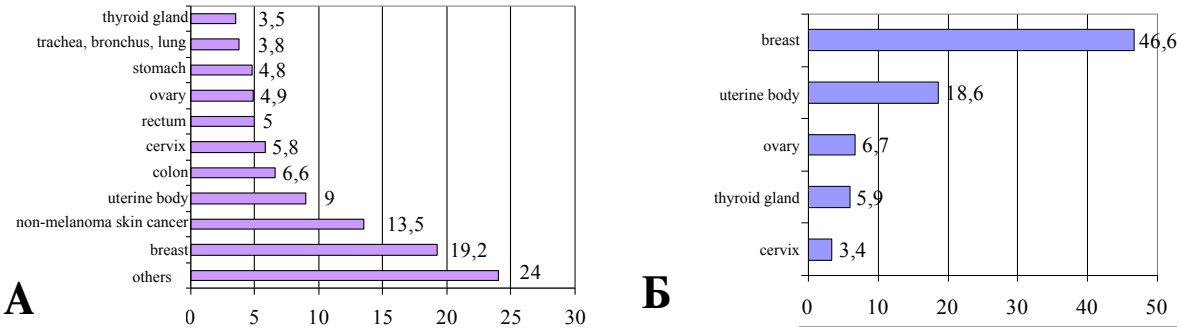


Fig. 2. The most common nosological forms of second cancers in breast cancer patients, %: A – in women of Ukraine; B – women of the research group.

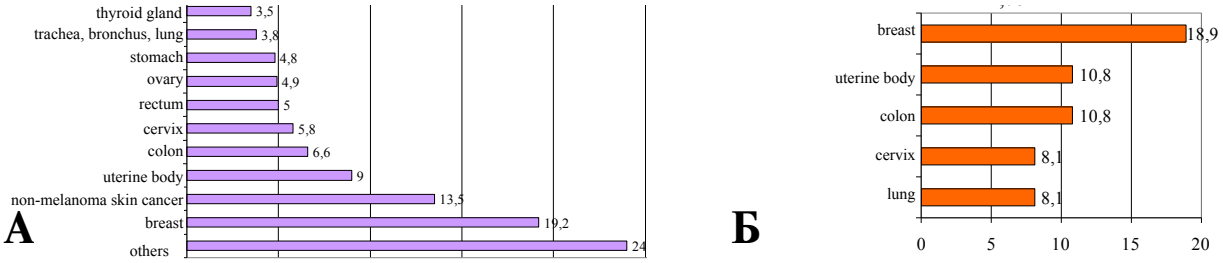


Fig. 3. The most common nosological forms of second cancers in patients with other forms of cancer, %: A – in women of Ukraine; B – women of the research group.

were predominantly women, the right part of the bulletin data chart is of interest. As can be seen from Fig. 2, in patients with the first breast cancer, the overwhelming majority of second cancers were breast MN (46.6%), in the second place – the uterine (18.3%), in the third – ovaries (6.7%), in the 4th and 5th places – the thyroid gland (5.9%) and the cervix (3.4%).

Among the patients of the analyzed group with second tumors in 17 patients, the primary cancer was thyroid cancer. In 9 of them (53%) the second cancers belonged to 10 most common nosological forms. These were breast cancer, the uterus and ovaries cancers and their percentages coincided (16.7%).

The distribution of nosological forms of second neoplasms in patients treated for cancer of the uterus seems quite logical within the framework of our hypothesis. In the first place, as before, there was breast cancer 38.5% (5 patients), in the second – lung cancer (23.1%, 3 patients), in the third – colon cancer (15.4%, 2 patients), in the fourth – cancer of the rectum (7.7%, 1 patients). The tactics of treating such patients involves radical surgical intervention, as a result of which the absence of such nosologies as cancer of the uterus, cervical cancer and ovarian cancer in the list of second neoplasms is quite obvious.

The nosological structure of the second MN in patients with cervical cancer is maximally approximated to the structure of the incidence of breast cancer in women in Ukraine: the first place occupies breast cancer (6 patients, 60%), the second – cancer of the uterus body (2 patients, 20%) and one case of lung cancer and melanoma.

Among the 8 patients treated for ovarian cancer and surviving to the second tumor, in five women (62.5%) the second tumor was in the breast, the remaining three women developed ovarian cancer, thyroid cancer and intestinal cancer (12 ,5 %).

Very limited (due to atypical nosology for treatment in the clinic of the Institute) was a sample of patients treated for MN of the rectosigmoidal junction. The nosological structure of the second cancers in this group of patients also corresponded to our hypothesis. Among only 5 patients, all three of the most common cancers were diagnosed: breast, uterine and cervical cancers.

The last diagram demonstrating the structure of second neoplasms for patients united in the category of "other first cancers" is quite indicative. The nosological forms presented in this category were significantly less frequent than those considered above (Figure 3). As can be seen, almost all nosologies from the top of the disease incidence diagram for women in Ukraine are also present here.

Similarly, to the nosological structure of the first cancers in the study group of patients, of which (structure) has been already mentioned above, the nosological structure of the second cancers also had a somewhat biased character in favor of "typical" forms for the clinic. In particular, there were no skin tumors in the analyzed data block and the number of patients with intestinal tumors was limited. Thus, initially the sample of those patients who have undergone treatment at the Institute and who had

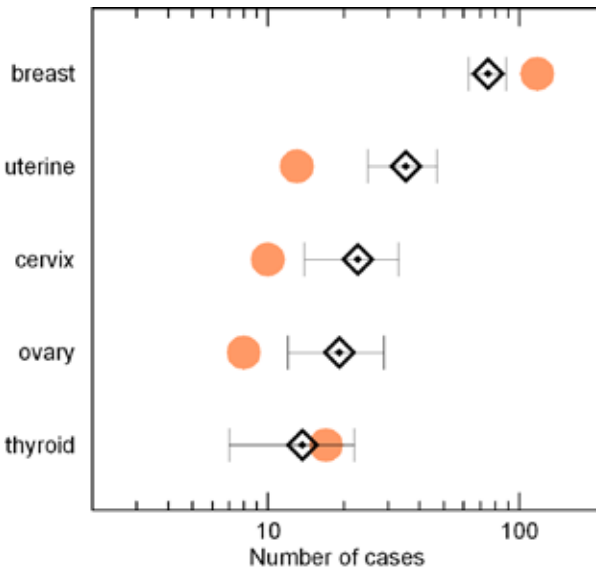


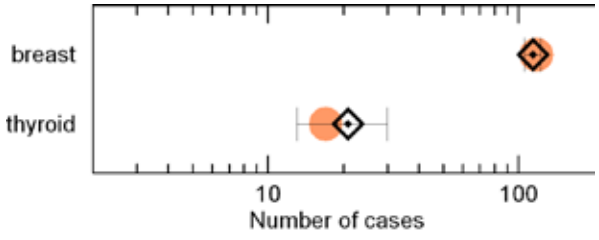
Fig. 4. Comparison of the actual number of cases of the primary cancer among 5 most common nosological forms with the expected number based on the MN incidence in Ukraine on this nosology.

second cancers after the treatment of the primary cancers was censored in nature, as not all patients returned to the Institute for the treatment of second cancers. In this regard, to verify the statistical significance of the results, the representativeness of the sample should be justified. To do this, in the study, for each of five most common nosological forms, a comparison was made of the actual number of cases of each cancer with the prediction of their number based on the disease incidence in Ukraine on this nosology.

Figure 4 illustrates the data for 166 patients with the primary cancer among five most common nosological forms. The circles show the actual number of cases of the primary cancer forms in this study, the rhombuses – the expected number of cases for the same nosological forms, calculated in accordance with the structure of the MN incidence in women in Ukraine, and the lines bounded by vertical strokes are formal 95% prediction intervals for stochastic scattering.

The figure clearly shows that the cancer of the uterus, cervix and ovarian cancer in the used

Fig. 5. Comparison of the actual number of cases of breast cancer and thyroid cancer with their expected number based on the MN incidence in Ukraine on this nosology.



data set are not representative and the number of these patients differs from national statistics in the direction to “less” and all the shifts are quite comparable. This is due to the fact that Kharkov is a major medical center in Ukraine, and patients have alternatives for choosing an institution to perform complex diagnostics and treatment of these nosologies. However, for treatment of breast cancer and thyroid cancer, the Institute is the leading medical establishment not only in Kharkov, but also in Ukraine.

Figure 5 shows that if we take into consideration only breast cancer and thyroid cancer and recalculate the national average of their frequencies, then the resulting ratio is ideally reproduced in the investigated dataset.

Similarly, Figures 6 and 7 compare the incidence of second cancers among five most common nosological forms for patients with the primary breast cancer with the predicted national averages of frequencies for the set of only these five forms.

As can be seen from Fig. 6, the frequencies of five identified nosological forms calculated for the Institute correspond fairly well to the average in Ukraine, and for two most representative nosological forms (Figure 7), the correspondence is within the expected stochastic variability.

It should be noted that the authors have also carried out a serious work to study the possible connection between the factors of treatment of the primary cancers (ionizing radiation, chemotherapy) and second tumors. At the same time, no direct correlation has been revealed.

Discussion

In the given study, the group of patients who have developed second tumors at distant post-treatment periods was divided into subgroups according to the nosological forms of the primary cancers. For each subgroup, the nosological structure of the second cancers was examined and compared with the official statistics. The conducted studies demonstrate that if we abandon the quantitative scale of measurement and move to the ordinal scale with the relations "more, less, equal to each other" then, in comparison with the structure of the MN in Ukraine, the order is not always preserved only on the last nosologies; this fact is quite understandable taking into account relatively low for this group absolute percentages.

Especially visually the obtained results are traced on a sample of patients with the primary breast cancer, since this cohort of patients is the most characteristic for the Institute's clinic and, accordingly, the most numerous. Unlike the

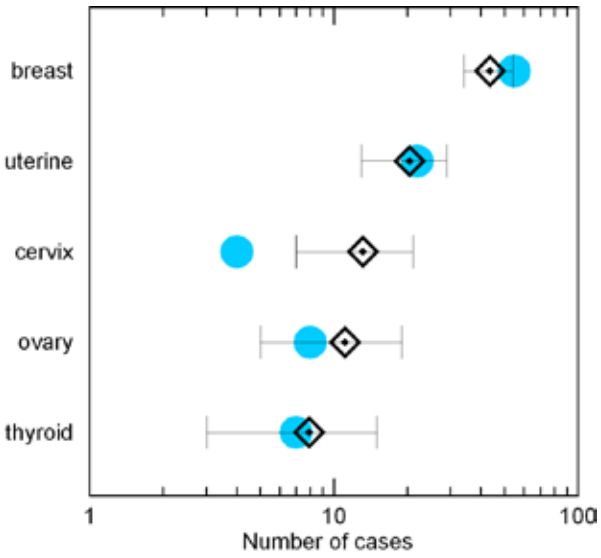
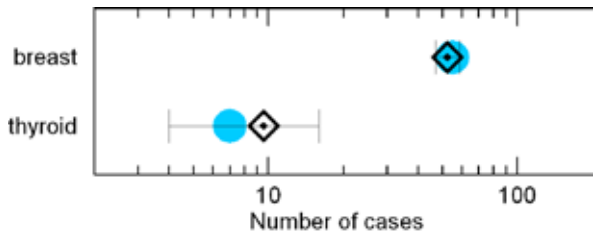


Fig. 6. Comparison of the cases number of 5 nosological forms of the second cancer for the primary breast cancer with the expected number of cases based on the MN incidence in Ukraine according on this nosology.

commonly held opinion that the most likely second cancer in case of this nosology is contralateral breast cancer [18], we have shown that not nosology determines the type of the second cancer, but its frequency in the structure of the overall incidence of the population. The necessary statistical processing has been carried out in the study to justify the representativeness of the sample being studied. For this purpose, for each of the nosological subgroups of the primary neoplasms, the actual number of cases of each cancer was compared with the prediction of their number based on the MN incidence in Ukraine for each nosology, in particular, for the breast. Besides, an additional argument for the representativeness of the studied sample is the comparison of our results with the SEER (Surveillance Epidemiology and End Results): among 328 691 clinical cases of the first breast cancer registered in SEER from 1973 to 2000, 182,057 cases were selected when patients have lived 5 or more years. The second tumor developed in 15 498 patients (8.5%), in particular, in 6491 (42%)

Fig. 7. Comparison of the actual number of cases of the second cancer from the number of nosological forms most fully represented in the studied dataset for the primary breast cancer with the expected number of them based on the MN incidence in Ukraine on this nosology.



cases it was cancer of the contralateral breast [3]. As can be seen from Fig. 2, in the sample that was used in our study, contralateral breast cancer developed in 46.6% of patients, that is, the results appeared to be very close. The discrepancy in the data in the direction to "more" in the studied sample is due to the fact that the overwhelming number of patients treated for the primary breast tumor in the Institute's clinic remain for further observation and are examined there, without addressing for the treatment of contralateral breast cancer to other medical institutions.

A fairly convincing argument is also the results of remote observations of 37 patients out of 203, in whom the second cancer did not belong to 5 most frequent nosological forms. Such cancers were categorized as "others" (ICD codes: C64, C91, C85, C81, C67, C64, C52, C51, C49, C44, C43, C37, C32, C20, C19, C18, C16). Analysis of the structure of second cancers also revealed the dominant of five basic nosological forms of the population structure.

Thus, it can be stated that the existing data set hasn't revealed statistically significant dependencies between treatment factors and the development of second cancers.

Attention is drawn to the fact that both primary tumors and second neoplasms are hormone dependent, and therefore we do not exclude that certain changes in the endocrine system are the basis of the revealed patterns. This conclusion, of course, is a priori and needs additional verification by means of an increase in the number of samples.

Conclusions

In this paper, the study results of s the relationship between the nosological forms of the primary and second neoplasms in patients who have undergone special treatment for oncological disease in the clinic of SE "Institute of Medical Radiology named after S.P. Grigoriev" of the National Academy of Medical Sciences of Ukraine and who have developed second cancers three and more years after the end of treatment.

In accordance with the specific weight of the nosological forms of the primary cancers, due mainly to the specialization of the Institute's clinic, the patients of the study group were divided into 5 nosological subgroups: patients with cancers of the breast, thyroid, uterine, cervical, ovarian and subgroup with other forms of cancers. For each of the subgroups, the nosological structure of the second cancers was investigated and compared with the overall structure of malignant neoplasms according to official statistics. It is shown that the frequencies of five allocated nosological forms calculated for the Institute correspond fairly

well to the population mean, while for two most representative nosological forms the correspondence is within the expected stochastic variability. Thus, it has been demonstrated that there are no statistically significant differences between the percentage composition of 10 major nosological forms of cancer in Ukraine and the structure of nosological forms of second cancers in the study group of patients.

The work was carried out in accordance with the research plan of SE "Institute of Medical Radiology named after S.P. Grigoriev" of the National Academy of Medical Sciences of Ukraine.
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Адрес для корреспонденции

61024, Украина,
г. Харьков, ул. Пушкинская, д. 82,
Институт медицинской радиологии
им. С.П. Григорьева,
группа медицинской информатики,
тел. раб.: +380 (67) 799-36-63,
e-mail: radzishevska@ukr.net,
Радзишевская Евгения Борисовна

Address for correspondence

61024, Ukraine,
Kharkov, Pushkinskaya str., 82,
SE «Institute of Medical Radiology
named after S.P. Grigoriev»,
Medical Informatics Group,
tel. office: +380 (67) 799-36-63,
e-mail: radzishevska@ukr.net,
Evgeniya B. Radzishevska

Сведения об авторах

Радзишевская Е.Б., к. ф.-м. н., руководитель группы медицинской информатики Государственного учреждения «Институт медицинской радиологии им. С.П. Григорьева» Национальной академии медицинских наук Украины, доцент кафедры медицинской и биологической физики и медицинской информатики Харьковского Национального медицинского университета.
Васильев Л.Я., к.м.н., главный врач Государственного учереждения «Институт медицинской радиологии им. С.П. Григорьева» Национальной академии медицинских наук Украины.
Книгавко В.Г., д.б.н., профессор, заведующий кафедрой медицинской и биологической физики и медицинской информатики Харьковского национального медицинского университета.
Луховицкая Н.И., к.м.н., научный сотрудник отделения ядерной медицины Государственного учереждения «Институт медицинской радиологии им. С.П. Григорьева» Национальной академии медицинских наук Украины.

Information about the authors

Radzishevska E.B., PhD, Head of the Medical Informatics Group of SE "Institute of Medical Radiology named after S.P. Grigoriev "of the National Academy of Medical Sciences of Ukraine, Associate Professor of the Department of Medical and Biological Physics and Medical Informatics of Kharkov National Medical University.
Vasil'ev L.Y., PhD, Head Physician of SE "Institute of Medical Radiology named after S.P. Grigoriev "of the National Academy of Medical Sciences of Ukraine.
Knigavko V.G., Doctor of Biological Sciences, Professor, Head of the Department of Medical and Biological Physics and Medical Informatics of Kharkov National Medical University.
Lykhovitskaya N.I., PhD, Researcher of the Nuclear Medicine Department of SE "Institute of Medical Radiology named after S.P. Grigoriev "of the National Academy of Medical Sciences of Ukraine.

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